Recent advances in mastocytosis and neoplasms of probable monocytic/dendritic cell lineage

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Abstract

In recent years, there has been a better appreciation of mast cell and monocyte/macrophage/histiocyte/dendritic cell ontogeny, which has led to reclassification of certain entities within the World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues. Notably, mastocytosis has been reclassified as a chronic myeloproliferative neoplasm, while the former "blastic natural killer cell lymphoma" or "haematodermic neoplasm" is now known as a blastic plasmacytoid dendritic cell neoplasm and classified with the acute leukaemias. This review aims to give a brief overview of the physiological roles and patterns of migration of the corresponding normal cells before discussing the presentation and diagnostic features of mast cell and monocyte/dendritic cell neoplasms. Distinguishing reactive from neoplastic proliferations still poses major challenges and the reasons for this are briefly explained.

Keywords clonality; dendritic cell; histiocytosis; mastocytosis; tumour

Introduction

Neoplasms of mast cell, monocyte or dendritic cell lineage are rare, but important to recognize and correctly subclassify, given their widely differing prognoses. The increasing use of lineage markers and an improved understanding of haematopoietic ontogeny have led to the reclassification of certain neoplasms in the WHO classification of tumours of haematopoietic and lymphoid tissues. In particular, the former ''blastic natural killer (NK) cell lymphoma'' or ''haematodermic neoplasm'' has been renamed blastic plasmacytoid dendritic cell neoplasm and classified with the acute leukaemias. Mastocytosis is now included in the chronic myeloproliferative neoplasms (CMNs), explaining its intermittent association with other CMNs and leukaemias.[1] This article describes the current classification of mast cell and histiocytic/dendritic cell (DC) neoplasms (Figure 1), highlighting new developments. It discusses the difficulties in separating neoplastic and reactive mast cell or histiocytic lesions and describes the normal functions and physiology of these cell types. Emphasis is placed on more common conditions, but very rare conditions, e.g., acute monoblastic leukaemia, are included for conceptual reasons. To help understand the behaviour of the corresponding neoplasms, the normal functions and distributions of the various cell types are discussed.

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Differentiation of haematopoietic cells

With the exception of follicular dendritic cells (FDCs) and the rather poorly characterized fibroblastic reticulum cells (FRCs), all histiocytic cells and mast cells are bone marrow derived and, like other leucocytes, develop from a common stem cell precursor that can also give rise to lymphocytes (Figure 1).[1] Early reports suggested that, in the mouse, plasmacytoid dendritic cells (pDCs) were derived from common lymphoid precursors.[2] However, recent studies suggest that both myeloid and plasmacytoid DCs, as well as mast cells, may be derived from a common myeloid precursor (Figure 1).[1–3] The CMNs are neoplastic clones recapitulating more mature myeloid cell types, while the acute myeloid and lymphocytic leukaemias, blastic plasmacytoid dendritic cell neoplasm and acute mast cell leukaemia recapitulate more primitive myeloid cell types (Figure 1). ''Histiocytic'' neoplasms recapitulate, with varying degrees of atypia, the phenotypes of more mature macrophages or DCs that are found outside bone marrow.[1]

Reactive and neoplastic proliferations can be difficult to separate

When a B- or T-cell neoplasm is suspected, it can sometimes be difficult to determine whether the lymphoid cells, are reactive or neoplastic, particularly if they show little atypia, e.g., mycosis fungoides and angioimmunoblastic lymphoma. Uniquely among mammalian cells, B and T cells have rearranged part of the genome at DNA level. This provides a unique tool with which to investigate whether the proliferation is clonal. In general, demonstration of clear-cut monoclonality is interpreted as an indication of neoplasia. For B-cell neoplasms light chain restriction determined by kappa and lambda immunostaining often suffices. For other B-cell and all T-cell neoplasms, polymerase chain reaction (PCR) for B-/T-cell receptor (B/TCR) rearrangements is required.[1] Mast cells and histiocytes only very rarely have rearranged B/TCR loci. Frequently, neoplastic mast cells and histiocytes show no greater atypia than their reactive counterparts, making distinction between reactive and neoplastic proliferations very difficult.[1,4–6] Occasionally, other techniques are used in an attempt to determine clonality, usually in a research setting. These include demonstration of the presence of a particular genetic aberration in all of the lesional cells and HUMARA.[7–9] However, if no particular genetic aberration can be identified, the first option is unavailable. Similarly, HUMARA relies on demonstrating non-random inactivation of the same X chromosome in all the cells of the lesion. It is therefore only possible in women who are heterozygous for at least one of a small number of genes on the X chromosome that show allelic polymorphism.[7–9] Clinicoradiopathological correlation may be helpful in suggesting the likely neoplastic potential of a lesion, but the neoplastic potential of some mast cell and histiocytic lesions remains undetermined. Mast cell and histiocytic proliferations arising in the absence of an obvious stimulus should be examined carefully in an attempt to determine whether they are neoplastic.[10]

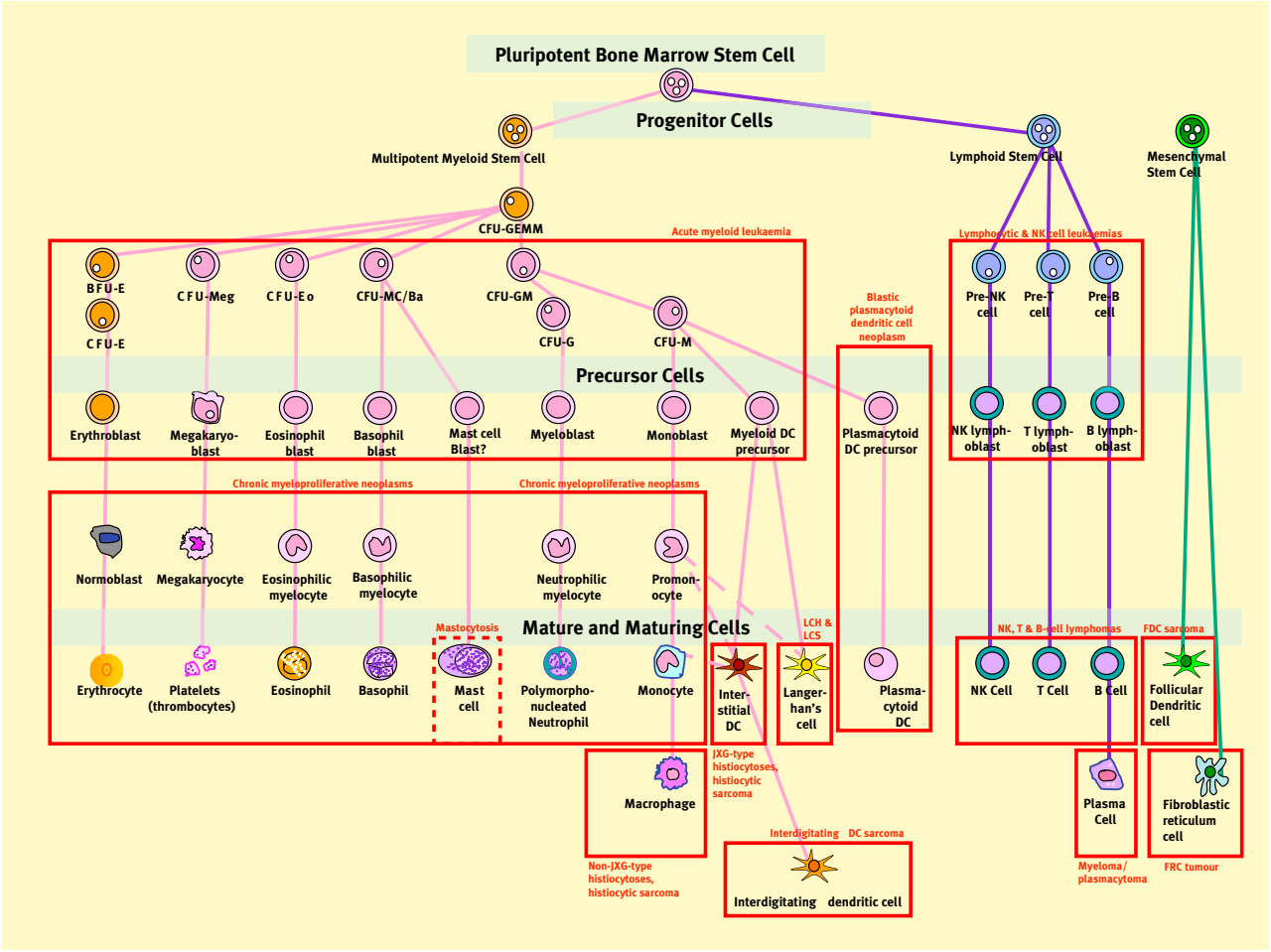

Figure 1 The differentiation pathways of haematopoietic cells are annotated in black, while the corresponding tumours are marked in red. Abbreviations: CFU — colony forming unit; BFU — blast forming unit; CFU-E — colony forming unit-erythroid; BFU-E — blast forming unit-erythroid; CFU-meg — colony forming unit-megakaryocyte; CFU-Eo — colony forming unit-eosinophil; CFU-MC/ba — colony forming unit-mast cell/basophil; CFU-GEMM — colony forming unit-granulocyte, erythroid, monocyte, megakaryocyte; CFU-GM — colony forming unit-granulocyte, monocyte; CFU-G — colony forming unit-granulocyte; CFU-M — colony forming unit-monocyte; DC — dendritic cell; NK — natural killer; JXG — juvenile xnathogranuloma; FRC — fibroblast reticulum cell; FDC — follicular dendritic cell; LCH — Langerhans cell histiocytosis; LCS — Langerhans cell sarcoma.

Mast cells

Normal mast cells

Mast cells are bone marrow-derived myeloid cells (Figure 1) with rather plastic morphology (Figures 2 and 3) scattered throughout most parts of the body. They are more numerous in skin, close to mucosal surfaces, in bone marrow and at sites of inflammation, particularly of an allergic nature.[11–13] They are often associated with lymphoplasmacytic lymphoma (LPL), particularly in the bone marrow (Figure 3),[14] where they may induce LPL proliferation via mast cell CD154 and neoplastic lymphoplasmacytic cell CD40 interactions.[15] Mast cells are closely related to basophils, found in blood, and may represent their tissue counterpart, just as macrophages are the tissue counterpart of monocytes. However, recent data suggest lineage divergence before the respective precursor cells leave the bone marrow.[11] Mast cell stimulation occurs when an antigen binds immunoglobulin E that is constitutively bound to FcER1 on mast cell plasma membranes, cross-linking the receptors. The binding of complement components C3a and C5a and various physical, chemical and immunological stimuli can activate mast cells. Activated mast cells degranulate, liberating histamine, serotonin, cytokines and various enzymatic and lipid-derived inflammatory mediators into their surroundings. These mediators initiate and perpetuate inflammation, as well as helping to determine the exact mix of cells present in the inflammatory infiltrate.[12]

Mastocytosis

Clinical features of mastocytosis: the majority of the symptoms and signs of mastocytosis are related to histamine release. Cutaneous manifestations include pruritus, urticaria, dermatographism, urtication and bulla formation. Histamine-induced vasodilatation may cause flushing, headache, syncope, hypotension. In the gastrointestinal system, abdominal pain and diarrhoea are related both to direct effects of histamine and to its propensity to increase gastric acid secretion, possibly leading to peptic ulceration. Gastrointestinal mast cell infiltrates and other